6 21 CFR §876.5820, Hemodialysis system and accessories.
7 21 CFR §876.5860, High permeability hemodialysis system.
10 21 CFR §876.5540, Blood access device and accessories .
8 21 CFR §876.5540, Blood access device and accessories.
9 21 CFR §876.5540, Blood access device and accessories.

Ultrafiltration Devices

A number of devices are used to perform ultrafiltration treatments. These include the filters, the pump systems used to manage the extracorporeal fluid flow, blood tubing sets, which make up the extracorporeal circuits, and blood access devices. The devices involved in ultrafiltration are presented below, along with a discussion of the regulation of these devices and of labeling considerations. As noted above, many of these devices are capable of performing a variety of modalities, including ultrafiltration. There are also a number of other devices and accessories that are necessary to perform ultrafiltration treatments, including blood tubing sets and blood access devices.

3.1 Device Descriptions and Regulations

Hemodialysis delivery systems and their accessories are described and classified in two sections of the Code of Federal Regulations (CFR). Under 21 CFR §876.5820, a conventional hemodialysis delivery system is defined as a system that "consists of mechanisms that monitor and control the temperature, conductivity, flow rate, and pressure of the dialysate and circulates dialysate through the dialysate compartment of the dialyzer." 6 Under 21 CFR §876.5860, a high permeability hemodialysis system is defined as a machine that contains an "ultrafiltration controller and mechanisms that monitor and/or control such parameters as fluid balance, dialysate composition, and patient treatment parameters (e.g., blood pressure, hematocrit, urea, etc.)."7

These classifications also contain ultrafilters, hemofilters, hemoconcentrators, and hemodialyzers, as well as their associated extracorporeal tubing lines. The discussions in this document and at the Advisory Panel meeting, however, will center on the filters and systems capable of performing ultrafiltration.

Both classifications above specify that dialysis delivery devices and accessories are Class II products and are thus appropriate for review and clearance under Premarket Notifications or 510(k)s. In performing the device reviews for 510(k)s, FDA compares the new proposed device to a "predicate" device (a device already cleared by FDA or one being marketed prior to the enactment of the Medical Device Amendments in 1976) in terms of safety and effectiveness to demonstrate substantial equivalence. These reviews include an evaluation of the devices' technological characteristics (device design and components), functional validation, and labeling.

Blood tubing for hemodialysis is regulated by the FDA under 21 CFR §876.5820, Hemodialysis system and accessories, and is a Class II device.

Blood access devices are regulated under 21 CFR §876. 5540, Blood access device and

accessories. This classification includes both, implanted and non-implanted (temporary) blood access devices. As defined in the code of federal regulations, implanted devices are Class III devices, while the temporary devices are Class II. In spite of the difference in their classification, both of these devices are currently reviewed and cleared under 510(k)s. In the future, Class III blood access devices may be down-classified to Class II, or the FDA may call for premarket approval (PMA) applications for these (i.e., they would remain as Class III devices, to be reviewed and approved under PMA's).

3.1.1 Filters

For the benefit of this discussion, a filter is defined as a cartridge or column containing a hollow-fiber, semi-permeable membrane, which is attached to an extracorporeal blood circuit so that blood may circulate through it for the purposes of its purification. Filters, as a general class of devices, consist of ultrafilters, hemofilters, hemodialyzers, hemoconcentrators, and hemodiafilters. Although different modalities of fluid removal or renal replacement may be performed, depending on the filters' design characteristics (see the Definitions and Nomenclature section of this package), all these devices share some basic design features. In use, for most filters in commercial distribution in the U.S., blood flows through the filter's hollow fibers (blood side), while dialysate, if utilized, flows outside the fibers (filtrate or dialysate side). Typically, the blood inlet and outlet ports are situated in line with the fibers of the filter, and the dialysate ports are placed perpendicular to the fibers. Counter-current flow is typically used.

A key part of the filter is its membrane, the material of which the filter's hollow fibers are manufactured. This membrane has a unique pore structure; a filter's permeability depends on pore size and arrangement. Filters featuring high permeability are typically used for ultrafiltration, hemofiltration, hemodiafiltration, and high-flux hemodialysis, while less permeable filters are generally employed in low-flux hemodialysis.

The design of the filter is also dependent on whether it is intended to handle dialysate. Since ultrafiltration and hemofiltration do not use hemodialysate circulation, what would be the dialysate inlet port is either not included, or capped off. The outlet from the filtrate side, typically placed perpendicular to the fibers, is provided so that the fluid removed from the patient can be directed to drain.

A filter's working parameters and performance specifications, including its surface area (total area available for fluid transfer), dimensions, permeability (ultrafiltration coefficient), solute clearance or sieving coefficient, resistance to flow in the blood and dialysate sides, and maximum allowable flow rates and transmembrane pressures, are clearly outlined in their labeling, so that clinicians may be able to select the best device for the therapy being performed.

3.1.2 CRRT and Conventional Dialysis Systems

The following is a list of components typically required of CRRT or conventional hemodialysis delivery devices:

Blood Pump – The blood pump is responsible for pumping the blood from the patients' arterial access, through the filter, and back to the patients' venous access. Typical blood pumps are designed to pump blood from 0 to 600 mL/min, and are monitored for accurate speed. During most alarm conditions, the blood pump is stopped to protect patient safety. Although some systems are capable of high blood flows (e.g., 600 ml/min), CRRT devices typically perform their treatments in the lower ranges of blood flow.

Dialysate Pump – The dialysate pump is responsible for pumping the dialysate fluid from its origination point through the dialyzer, and back to waste. Typical dialysate pumps are designed to pump blood from 0 to 800 mL/min, and are monitored for accurate speed. During most alarm conditions, the dialysate pump is stopped to protect patient safety.

Anticoagulant Pump – An anticoagulant pump, usually in the form of a small stepper motor with a syringe, is required to administer anticoagulant (e.g. heparin or sodium citrate) to the patient. This component may be intrinsic to the CRRT or conventional dialysis system, or a separate, stand-alone pump may be used.

Ultrafiltration (UF) Controller – An ultrafiltration controller is required to ensure adequate patient fluid balance in all fluid removal or renal replacement therapies, except low-flux hemodialysis. The UF controller uses data supplied from the blood pump, dialysate pump, pressure monitoring system, and/or scales to control the amount of excess fluid that is removed from the patient during each dialysis session.

Pressure Monitoring System – CRRT and hemodialysis delivery devices contain multiple pressure transducers in order to monitor the operating pressure of the blood and dialysate. Generally, the patients' venous pressure is measured, along with the transmembrane pressure of the filter. Arterial pressure is also frequently measured.

Air Detection System – An air detection system is required after the blood pump to ensure that an air embolus is not returned to the patient. If an air embolus is detected, the device alarms and the blood pump is stopped.

Blood Leak Detector – A blood leak detector measures the color of the dialysate fluid or filtrate exiting the filter or hemodialyzer and alarms if blood is detected. The presence of blood in the dialysate fluid or filtrate signals a leaking filter.

Temperature Monitor – Hemodialysis delivery systems have temperature transducers to measure the temperature of the dialysate.

Disinfection System – Any hemodialysis delivery system that has dialysate supplied from a central supply, or contacts patient fluid (including ultrafiltrate) must be periodically disinfected. The CRRT and hemodialysis delivery system is responsible for ensuring that adequate disinfection parameters (e.g. disinfection mix time, temperatures, etc.) are established. Hemodialysis

delivery systems that use closed systems, and do not directly contact patient fluid, are not responsible for disinfection.
User Interface – CRRT and Hemodialysis delivery systems are software-controlled devices, and require a user interface for entering the prescription information, monitoring treatment, and communicating alarms. Most modern systems contain sophisticated interfaces that display treatment times, operating pressure, remaining time left, ultrafiltration rate, volume of fluid removed, etc. The user interface may be text based, or may be designed as a graphical, touch-screen display. The user interface can be designed to limit certain features based on passwords in order to prevent misuse, and it can also be designed to assist in setup and trouble-shooting of the device by giving the user of the device clear visual instructions on-screen. In this capacity, the interface works in conjunction with the labeling of the device (e.g., Operator's Manual). The user interface of any hemodialysis delivery system should be designed with human factors in mind.

Labeling – A comprehensive Operator's Manual must be included with every CRRT or conventional hemodialysis delivery system. This manual should demonstrate the proper setup and use of the device, as well as how to respond to any alarm conditions.

Blood rinse-back – A fail-safe design allowing blood rinse-back, either using battery backup power or mechanical means, in the case of power failure.

In addition, depending on the design of the device, a CRRT or conventional hemodialysis system may include the following components, although these pertain to the preparation and/or handling of dialysate, and are therefore not used in ultrafiltration therapies. They are mentioned here for background purposes, but will not be discussed further in this package.

Fluid Heater – Some hemodialysis delivery systems contain built-in fluid heaters to warm dialysate to physiologic temperatures, while other systems use fluid heaters as an optional accessory. Systems that use a heater as an accessory may have electrical interfaces with the heater, or these heaters may be independent. Any system with a fluid heater should also contain temperature monitors to prevent fluid over-heating.

Conductivity Monitor –systems that mix the dialysate fluid online to be used for a treatment must have a conductivity meter and a pH sensor to ensure that the dialysate composition is adequate.

pH Sensor – See the conductivity meter description above.

Water Treatment System – Some hemodialysis delivery devices have built-in water treatment systems to purify water so that it may be suitable to be mixed with dialysate concentrates and produce dialysate for use within the treatment.

Scales – Hemodialysis delivery systems that use pre-mixed dialysate may have scales to monitor the amount of dialysate remaining and the amount of dialysate that has been used. These scales can interface with the UF controller to ensure that the proper amount of fluid has been removed from the patient.

Hemodialysis delivery devices monitor ongoing treatments, and provide visual and audible

alarms in the event of an unsafe situation. These devices typically prioritize alarms in order to ensure that the most serious problems are addressed by the user first. Often, the system will have different levels for alarms conditions. For instance, a high return pressure may first trigger a “Caution” at a designated level, and then a “Warning” alarm at a higher lever.

Alarms present on hemodialysis delivery devices may include the following:

Pressure alarms – Blood pressure alarms are present for both over-pressure and under-pressure situations. In addition, the dialysate pressure is monitored, and an alarm is triggered if the transmembrane pressure exceeds safe levels.

Temperature alarms – Temperature alarms are triggered if the incoming dialysate fluid is higher or lower than pre-set limits.

Blood leak alarm – As discussed above, blood leak alarms monitor the spent dialysate or filtrate for the presence of blood, and respond accordingly.

Air embolism alarm – As discussed above, air embolism alarms monitor the venous return line of the blood tubing for air embolism, and respond accordingly.

Vascular access disconnect alarms – Vascular access disconnect alarms monitor the status of the patients return access, to ensure that needle pull-out or catheter disconnection has not occurred. Most current systems rely on the venous return pressure to monitor for vascular disconnect, since disconnection should result in a noticeable drop in venous pressure. However, inherent resistance in the blood tubing and small gauge needles can cause enough back-pressure in the system to prevent the venous return pressure alarm from triggering. This situation could result in significant blood loss and eventual exsanguination of a patient. Other systems rely on single-needle modes of dialysis, so that a venous access disconnect would be detected by air embolus detectors. Vascular access disconnections remain one of the more serious risks of performing extracorporeal blood therapies.

Conductivity / pH alarms – Hemodialysis delivery systems that proportion purified water with dialysate concentrate are required to have conductivity and pH alarms to ensure that the resulting dialysate does not fall above or below pre-set limits.

Water quality alarms – Hemodialysis delivery systems that include a water treatment component should contain alarms to indicate that the water quality has not met the required purity standard.

System level alarms – System level alarms are designed to alert the user of device hardware and/or software issues.

3.1.3 Isolated Ultrafiltration Systems

Isolated ultrafiltration systems are a subset of the pump systems described above. Because isolated systems are only designed to perform one or two modalities, they tend to be simpler, with fewer operator controls, monitors and capabilities. Also, compared to CRRT or conventional

dialysis systems, which require additional components to perform the variety of modalities for which they are labeled, isolated systems are typically smaller in size, thus making them more portable. Their design specifications and capabilities are reflected in the device labeling.

Since these devices do not handle dialysate, they do not include those components used with dialysate, such as proportioning systems, conductivity and pH meters and alarms, and fluid heaters. Also, they do not require connection to a water or dialysate supply. However, they still require basic safety features, such as air detection, blood leak monitoring, and blood and ultrafiltrate pressure monitoring.

3.1.4 Accessory Devices

Below is a brief listing of additional devices that may be required to perform ultrafiltration. This listing does not include basic medical supplies such as gauze, access needles, tape, or other such items. In addition, this listing does not include any anticoagulant that may be prescribed (e.g., heparin or sodium citrate). Again, the discussion in this document and at the Advisory Panel meeting will center on ultrafiltration devices, although information on these accessories is valuable for background purposes.

3.1.4.1 Blood Tubing

Hemodialysis blood tubing is sterile tubing designed to route the patient's blood from the arterial access, through the filter or hemodialyzer, and back to the patient through their venous access. This tubing, which is typically constructed from polyvinyl chloride (PVC), is designed to interface with specific pump systems. Depending on the pump system used, this tubing may contain the following components: arterial and/or venous drip chambers, infusion ports, infusion tubing lines, tubing lines for pressure monitoring, and transducer protectors designed to prevent patient blood from contacting the pressure transducer. Proper setup of this blood tubing is crucial, since the hemodialysis delivery system typically relies on proper tubing placement for pressure monitoring, blood leak detection, and monitoring of venous air embolism. Also, improper placement may cause kinks and obstructions, which can lead to hemolysis.

Blood tubing can also come in pre-formed sets, or cartridges. This type of tubing reduces the number of connections that the operator is required to perform. These cartridges can be supplied with or without a pre-attached filter or hemodialyzer.

3.1.4.2 Blood Access Devices

As defined in the code of federal regulations, "a blood access device and accessories is a device intended to provide access to a patient's blood for hemodialysis or other chronic uses." 8 This classification includes both implanted and non-implanted (temporary) access devices. Implanted devices, which are Class III devices, consist of "various flexible or rigid tubes, which are surgically implanted in appropriate blood vessels, may come through the skin, and are intended to remain

in the body for 30 days or more." 9 These devices feature textile cuffs, which allow tissue ingrowth at the implantation site. A temporary device "consists of various flexible or rigid tubes, such as catheters, cannulae or hollow needles, which are inserted into appropriate blood vessels or a vascular graft prosthesis (§870.3450 and §870.3460), and are intended to remain in the body for less than 30 days." 10 Fistula needles are included in the temporary device category.

Depending on their dimensions, design characteristics and labeling, blood access devices may be placed on peripheral veins or central veins. Also, these devices may feature two or three lumens. In extracorporeal circuits, a dual-lumen access device may be used to provide arterial and venous blood flow, with the third lumen in a triple lumen device being used for infusion. It is important to note that, although very similar in design to central venous infusion catheters (i.e., central catheters labeled for infusion and not for dialysis), central catheters to be used in hemodialysis applications should be specifically labeled for such use.

3.2 Indications for Use and Labeling Considerations

The labeling, specifically the indications for use, cleared for some of the devices that can be used to perform ultrafiltration is discussed below. FDA asks the panel to keep these labeling considerations in mind when making recommendations regarding the possible labeling of ultrafiltration systems for specific use in heart failure. As has been pointed out, no ultrafiltration devices have been approved or cleared by FDA labeled specifically for use in the treatment of heart failure.

3.2.1 Ultrafilters and Hemofilters

As mentioned earlier, historically, the FDA has cleared ultrafilters and hemofilters as general tools for the removal of excess fluid from volume overloaded patients. These devices have been marketed for many decades.

As an example, the Minntech Minifilter Plus™, which received FDA clearance under K962707, states in its indications for use that:

The Minifilter Plus Hemofilter Kit is used in prevention or relief of fluid overload, electrolyte and acid/base imbalances in cases of acute renal failure with oliguria or anuria. Also, congestive heart failure, pulmonary and cerebral edema, anasarca, ascites, septic shock, burns etc.

In hypervolemic patients requiring parenteral nutrition and/or large volume of parenteral medications, the hemofilter may be used to reduce fluid overload.

In hypercatabolic patients requiring more intensive solute removal, a sterile dialysate fluid can be made to flow around the fibers via the dialysate ports, to increase clearance of small molecules.

3.2.2 Hemodialyzers

For reference, a typical hemodialyzer indications for use statement is given here (Gambro Polyflux 14L, 17L and 21L hemodialyzers, as cleared under K040255):

The capillary dialyzer is intended for use in hemodialysis for the treatment of chronic and acute renal failure.

3.2.3 CRRT Systems

CRRT systems do have labeling for use in ultrafiltration treatments. Ultrafiltration is only one of several modalities that these devices can perform.

The Prismaflex™ System, which was cleared under K041005 states in its indications for use:

The Prismaflex is indicated for the following use:

Continuous solute and/or fluid removal in patients with acute renal failure or fluid overload.

All treatments administered by the Prismaflex must be prescribed by a physician.

Although the indications for use statement for this CRRT device do not list all the modalities it can perform, including ultrafiltration, these are listed in the Operator's Manual.

Similarly, another CRRT system, the B.Braun Diapact is labeled as follows (as cleared under K973322):

Diapact is an extracorporeal blood purification system intended to be used for acute renal failure. The system provides high flow continuous renal replacement therapies, emergency intermittent dialysis treatment and plasmapheresis.

3.2.4 Conventional Hemodialysis Systems

Several conventional hemodialysis systems are currently on the market. They have similar labeling. For example, the Fresenius 2008K System, cleared under K994267, states in its labeling:

The Fresenius 2008K is indicated for acute and chronic dialysis therapy.

Similarly, the NxStage System One, which was cleared for marketing under K030470, is:

The NxStage System One is indicated for treatment of renal failure or fluid overload using hemofiltration, hemodialysis and/or ultrafiltration. All treatments must be administered by a

health care provider, under physician prescription.

It should be noted that this NxStage device is somewhat different in its design and labeling and can be considered to be somewhere in between an isolated ultrafiltration system and a conventional hemodialysis system. In fact, when first cleared for marketing, the NxStage system was only labeled to perform hemofiltration, which would have placed it among the isolated treatment systems. As originally cleared under K001283, the NxStage device, which was named the LifeMate™ Hemofiltration System at that time, was labeled as follows:

The LifeMate™ Hemofiltration System is indicated for treatment of renal failure or fluid overload using hemofiltration and/or ultrafiltration. All treatments must be administered by a health care provider, under physician prescription.
The NxStage System One remains smaller and more portable than the CRRT and conventional hemodialysis systems discussed above, even after the addition of the hemodialysis modality.

3.2.5 Isolated Systems

To date, only one system has been cleared for marketing as an isolated ultrafiltration system. This is the CHF Solutions Aquadex FlexFlow™ System, which has also been previously called the CHF Solutions System 100. This system is only designed and labeled for ultrafiltration; it does not perform hemodialysis or any other renal replacement modality. As can be seen, it is also not currently labeled for use in renal replacement.

As most currently cleared, under K050609, the Aquadex FlexFlow™ System is labeled as such:

The Aquadex FlexFlow™ System is indicated for:

Temporary (up to 8 hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy, and

Extended (longer than 8 hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy and require hospitalization.

All treatments must be administered by a health care provider, under physician prescription, both of whom having received training in extracorporeal therapies.